

**REMARKS**

The specification and claim 3 have been amended to correct minor typographical and/or grammatical errors. At page 1 of the specification, the cross reference to related applications has also been amended to reflect the status of the provisional application from which the present application claims priority. Claims 5 and 10-12 have been canceled. No new matter has been added.

The June 17, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments, the Declaration of James Mullin presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

At page 2 of the Official Action, the Examiner objects claims 3 and 11 and the specification for a number of typographical and/or grammatical errors. These errors have been corrected in accordance with the present amendment. Applicants have also corrected the cross reference to the related provisional application.

At page 3, the Examiner indicates that the previously submitted oath/declaration is defective. A substitute oath/declaration is therefore submitted herewith, which renders this objection moot.

At page 4, the Examiner rejects claims 3-12 under 35 U.S.C. §101 as the claimed invention is allegedly not supported by a substantial utility. Additionally, at page 6, the Examiner uses this lack of utility rejection to form the basis for a rejection of claims 3-12 under 35 U.S.C. §112, first paragraph, as one skilled in the art would allegedly not know how to use the claimed invention.

At page 6, the Examiner rejects claims 3-12 under 35 U.S.C. first paragraph, as the specification allegedly fails to describe the subject matter claimed in such a way as to enable one skilled in the art to make and/or use the invention.

Finally, at page 11, the Examiner rejects claims 3-12 under 35 U.S.C. §112, first paragraph, asserting that the specification allegedly fails to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The foregoing constitutes the entirety of the objections and rejections raised in the June 17, 2003 Official Action. In light of the present amendments, the Declaration of Dr. Mullin, and the following remarks, each of the above-noted objections and rejections under 35 U.S.C. §§ 101 and 112, first paragraph, is respectfully traversed.

**Claims 3, 4, and 6-9 as Presently Amended Fully Comply with the Utility Requirement Set Forth in 35 U.S.C. §§101 AND 112, First Paragraph**

At page 5 of the Official Action, the Examiner relies on Clarke et al., *Advanced Drug Delivery Reviews* 2000;41:283-301, for the assertion that the claimed invention is a potential invention. The Examiner also cites the present specification for the teaching that functional verification of tight junction (TJ) leakiness in upper gastrointestinal (GI) precancerous states in humans is necessary to practice the method as claimed. The Examiner then concludes that the claimed invention does not have substantial utility.

Applicants respectfully disagree with the forgoing assertions for the following reasons. The claims as presently amended are directed to a method for diagnosing Barrett's

esophagus in a patient free of ulcerative disease of the GI tract comprising measuring levels of at least one carbohydrate, e.g., sucrose, in the patient's urine sample. The claimed method may further comprise a biopsy step for examining TJ leakiness of a esophageal mucosal sample from the patient. At page 8 of the specification, it is disclosed that aberrant TJ or TJ leakiness is associated with tumors and transformation. At page 14, lines 17-33, it is disclosed that sucrose is an excellent marker for TJ leakiness in the upper GI tract and that a defect in the gastric barrier would enable sucrose to diffuse undegraded into the bloodstream which allows its subsequent quantitative appearance in blood and then urine. Accordingly, the specification as originally filed, provides evidence of the correlation between TJ leakiness, indicated by elevated urine sucrose levels, and precancerous conditions, e.g., Barrett's esophagus.

Moreover, Applicants respectfully submit herewith a Declaration of James Mullin, providing additional experimental data evidencing the utility of assessing urine levels of sucrose for diagnosing Barrett's esophageal conditions in a patient. Specifically, the data presented in the Declaration demonstrate that patients having Barrett's esophagus (Mean = 153 mg  $\pm$  93 mg  $\pm$  30 mg) present with significantly higher urine sucrose levels than those control patients who are free of reflux and Barrett's esophagus (non endoscoped control: Mean = 66 mg  $\pm$  13 mg  $\pm$  7 mg; endoscoped control: Mean = 60 mg  $\pm$  25 mg  $\pm$  11 mg) and those patient with reflux only (Mean = 82 mg  $\pm$  42 mg  $\pm$  13 mg). These experimental data clearly demonstrate that Barrett's esophagus, a precancerous condition of the esophageal mucosa, is correlated with TJ leakiness, indicated by increased urine sucrose levels.

In summary, the utility of the instantly claimed invention is specific, substantial, and credible. Accordingly, the

rejection of claims 3, 4, and 6-9 as allegedly lacking utility under 35 U.S.C. §101 is clearly improper and should be withdrawn.

At page 6 of the Official Action, the Examiner further rejects claims 3, 4, and 6-9 under 35 U.S.C. §112, first paragraph asserting that the claimed invention is not supported by a substantial utility.

Applicants respectfully direct the Examiner's attention to MPEP §2107.01 which provides:

Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper.

In the instant case, as evidenced by the experimental data provided in the Declaration of James Mullin submitted herewith, the claimed invention is supported by specific, asserted, and well established utility. Therefore, the Examiner's rejection of claims 3, 4, and 6-9 under 35 U.S.C. 112, first paragraph, for an alleged "lack of utility" is untenable and should be withdrawn

**Claims 3, 4, and 6-9 as Presently Amended are Fully in  
Compliance with the Enablement Requirement Set Forth in 35  
U.S.C. § 112, First Paragraph**

At pages 8 and 9 of the Official Action, the Examiner, again, cites Clarke et al. and the present specification for the teaching that the claimed invention is merely a potential invention and that the functional verification of TJ leakiness in upper GI precancerous states in humans is necessary to practice the claimed method. At page 10, the Examiner further cites Tockman et al., *Cancer Research* 1992;52:2711s-2718s, as

teaching that early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening. The claimed method is clearly **evidenced and validated** by the data presented in the Declaration of James Mullin, i.e; elevated urine sucrose levels, an indication of TJ leakiness, are correlated with the presence of Barrett's esophagus, a precancerous condition, in patients.

Applicants also traverse the Examiner's assertion, at page 11, that "given the simplicity of the basic assay, that is the assay of sucrose in urine which is well known in the art, one would wonder why the claimed assay has apparently not been done". It is submitted that the issue here is whether the claimed invention is enabled by the specification, not the state of complexity of the technology. Moreover, it is improper to conclude a claimed invention lacks enablement based on the fact that the technology is simple and no one else has yet used the technology before.

Also at page 11, the Examiner states that no working example or evidence has been provided by the specification as how to practice the claimed invention. Applicants respectfully submit that this assertion is erroneous. As discussed above, at pages 8-14 of the specification, it is disclosed that TJ leakiness is correlated with tumors and transformations and that elevated urine levels of sucrose is correlated with TJ leakiness in upper GI. Also provided in the Declaration of James Mullin, is data showing that urine sucrose levels are significantly elevated in patients with Barrett's esophagus, a precancerous condition. Moreover, at page 5, line 29, over to page 6, line 7, and page 14, lines 17-33 of the specification, examples of assessing TJ leakiness by measuring urine sucrose levels in patients are provided, wherein patients are given 200 ml of

0.5g/ml sucrose for oral administration and sucrose levels in the urine sample collected overnight post sucrose administration are measured. Therefore, both evidence and guidance in practicing the claimed invention are fully disclosed by the specification as originally filed.

Finally, at page 14, the Examiner asserts that the specification fails to define the term "precancerous" and that although Barrett's esophagus is known to predispose some patients to malignancy, not all of the patients with Barrett's esophagus develop adenocarcinoma. The Examiner further states that the claimed method of diagnosing the broadly claimed precancerous condition is not commensurate in scope with the disclosure in the application. Applicants disagree with this notion. However, to expedite the prosecution, claims 3, 4, and 6-9 have been amended to recite "a method of diagnosing Barrett's esophageal condition in a patient".

In view of the Declaration of James Mullin and the disclosure in the specification, Applicants submit that the claimed invention is fully enabled. Accordingly, withdrawal of the rejection of claims 3, 4, and 6-9 under 35 U.S.C. §112, first paragraph is respectfully requested.

#### **CONCLUSION**

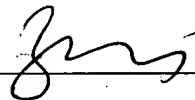
In view of the amendments, the Declaration of James Mullin, and the remarks presented herewith, it is respectfully urged that the rejections set forth in the June 17, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the

Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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Enclosure:

- Substitute oath/declaration;
- Declaration of James M. Mullin under 37 C.F.R. §1.132; and
- CV of James M. Mullin.